Tetrahedron. Vol. 26, pp. 3271 to 3277. Pergamon Press 1970. Printed in Great Britain

LAURINTEROL, DEBROMOLAURINTEROL AND ISOLAURINTEROL, CONSTITUENTS OF *LAURENCIA INTERMEDIA* YAMADA[1]

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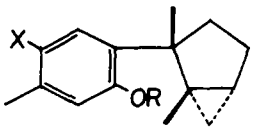
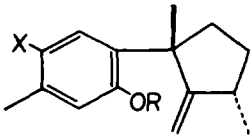
(*Received in Japan* 9 *February* 1970; *Received in the UK for publication* 1 *April* 1970)

Abstract—A new type of sesquiterpenoid containing bromine and its debromo analog, laurinterol (I) and debromolaurinterol (II), as well as an isomeric bromo compound, isolaurinterol (III), have been isolated from *Laurencia intermedia* Yamada (Rhodomelaceae), and their structures determined.

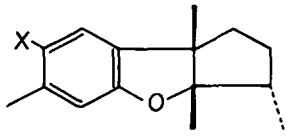
RECENTLY it has been reported, in a preliminary communication,[2] that a new type of sesquiterpenoid containing a Br atom and the corresponding debromo compound, isolated from *Laurencia intermedia* Yamada (Japanese name: "Kurosozo"; Rhodomelaceae) and designated as laurinterol and debromolaurinterol, are represented by (planar) structures I and II, respectively. The present paper deals with the full details of the isolation and structural elucidation of laurinterol, debromolaurinterol as well as a new bromo compound, isolaurinterol (III), which has been isolated from the same alga as a minor component.



I: X = Br, R = H
Ia: X = Br, R = Ac
II: X = R = H
IIa: X = H, R = Ac



III: X = Br, R = H
IIIa: X = Br, R = Ac
IV: X = R = H
IVa: X = H, R = Ac



V: X = Br
VI: X = H

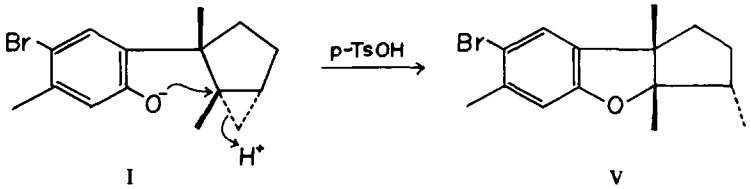
The air dried seaweed was extracted with methanol and the methanol soln was concentrated *in vacuo* to leave a resinous substance, which was then percolated with ether. The ether soln was washed successively with dil KOH soln, dil HCl and water, and the neutral fraction thus obtained was chromatographed on alumina. The fraction eluted with n-hexane–benzene (5:1) consisted of a mixture of phenolic compounds.* This fraction was repeatedly rechromatographed over silica gel to yield I, $C_{15}H_{19}OBr$, and II, $C_{15}H_{20}O$, as colourless crystals melting at 54–55°, $[\alpha]_D$ +13·3°, and colourless oil, $[\alpha]_D$ −12·2°, respectively.

The isolation and purification of I and II were achieved more conveniently via their acetates Ia and IIa, and an isomeric bromo compound named isolaurinterol (III), $C_{15}H_{19}OBr$, was newly isolated by this procedure. Thus, the mixture of phenolic

* These phenols could not be obtained from dil KOH soluble part of the extracts.

compounds mentioned above was acetylated with acetic anhydride and pyridine in the usual manner and the product was chromatographed on silica gel. The n-hexane–benzene (3:1) eluate afforded laurinterol acetate (Ia), $C_{17}H_{21}O_2Br$, m.p. 93–93·5°, $[\alpha]_D$ +11·1°, as colourless crystals and the n-hexane–benzene (1:1) debromolaurinterol acetate (IIa), $C_{17}H_{22}O_2$, $[\alpha]_D$ −28·9°, as colourless oil. Acetate of the minor component, isolaurinterol acetate (IIIa), $C_{17}H_{21}O_2Br$, $[\alpha]_D$ −70°, was isolated from the n-hexane–benzene (10:1) eluate. Mild hydrolysis of these acetates, Ia, IIa and IIIa, regenerated the corresponding free phenols, I, II and III, respectively.

Laurinterol (I), M^+ 296 and 294, indicated in its UV, IR and NMR (Fig 1-A) spectra the presence of a trisubstituted phenol group [λ_{max} 225, 283 and 289 mμ (ε 7100, 2200 and 2100); ν_{max} 3600, 1610, 1495 and 1152 cm^{-1}; τ 5·14 (1H, s; OH), 3·58 (1H, s) and 2·53 (1H, s)], an aromatic Me group [τ 7·78 (3H, s)], two tertiary Me groups [τ 8·71 and 8·66 (each 3H, s)] and a cyclopropane ring [ν_{max} 3060 and 1025 cm^{-1}; τ 9·48 (2H, br. d, J = 6·5 c/s) and ca. 8·9 (1H, m)]. These spectral data and the mass spectrum (see below) suggested that I would have a structure similar to that of aplysin (V)[3] except an OH group and a cyclopropane ring moiety. Treatment of I with *p*-toluenesulfonic acid gave an isomeric ether, $C_{15}H_{19}OBr$, m.p. 85–86°, $[\alpha]_D$ −86·1°, in a good yield. This ether has now been identified as aplysin (V) by the mixed m.p. and by a comparison of the IR (Nujol) and NMR spectra with those of an authentic specimen. Both this transformation and the spectral data unambiguously determined the positions of the relevant substituents in the aromatic nucleus as well as the presence of a dimethylbicyclo[3.1.0]hexane group in laurinterol. Thus, the structure of laurinterol should be represented as I. The absolute configuration of laurinterol acetate (Ia) has been determined using the X-ray diffraction method.[4]



I V

Debromolaurinterol (II), M^+ 216, a new sesquiterpene phenol, in its IR spectrum exhibited bands at 3060 and 1020 cm^{-1} characteristic of cyclopropane and at 3580, 1130 and 955 cm^{-1} due to disubstituted phenol grouping. Its NMR spectrum (Fig 1-C) displayed the signals comparable with those of I at the higher magnetic field region [τ ca. 9·5 (2H, m), ca. 8·9 (1H, m), 8·71 (3H, s), 8·65 (3H, s) and 7·80 (3H, s)], suggesting that II would have the same carbon skeleton as I. In the lower field region, however, the distinct difference was observed; i.e., in the spectrum of II, absorptions due to three aromatic protons appeared at τ 3·70 (1H, br. s), 3·51 (1H, br. d, J = 7·5 c/s) and 2·77 (1H, d, J = 7·5 c/s). Hence, this phenol II must be a debromo analog of laurinterol. This was confirmed on the basis of the conversion of II into Ia by treatment with bromine in acetic acid followed by acetylation as well as the reduction of I to II with LAH. Treatment of II with *p*-toluenesulfonic acid in acetic acid led to a good yield of formation of debromoaplysin (VI).[5]

As mentioned above, a new bromo compound, isolaurinterol acetate (IIIa), M^+ 338 and 336, was isolated as colourless oil in low yield from the n-hexane–benzene

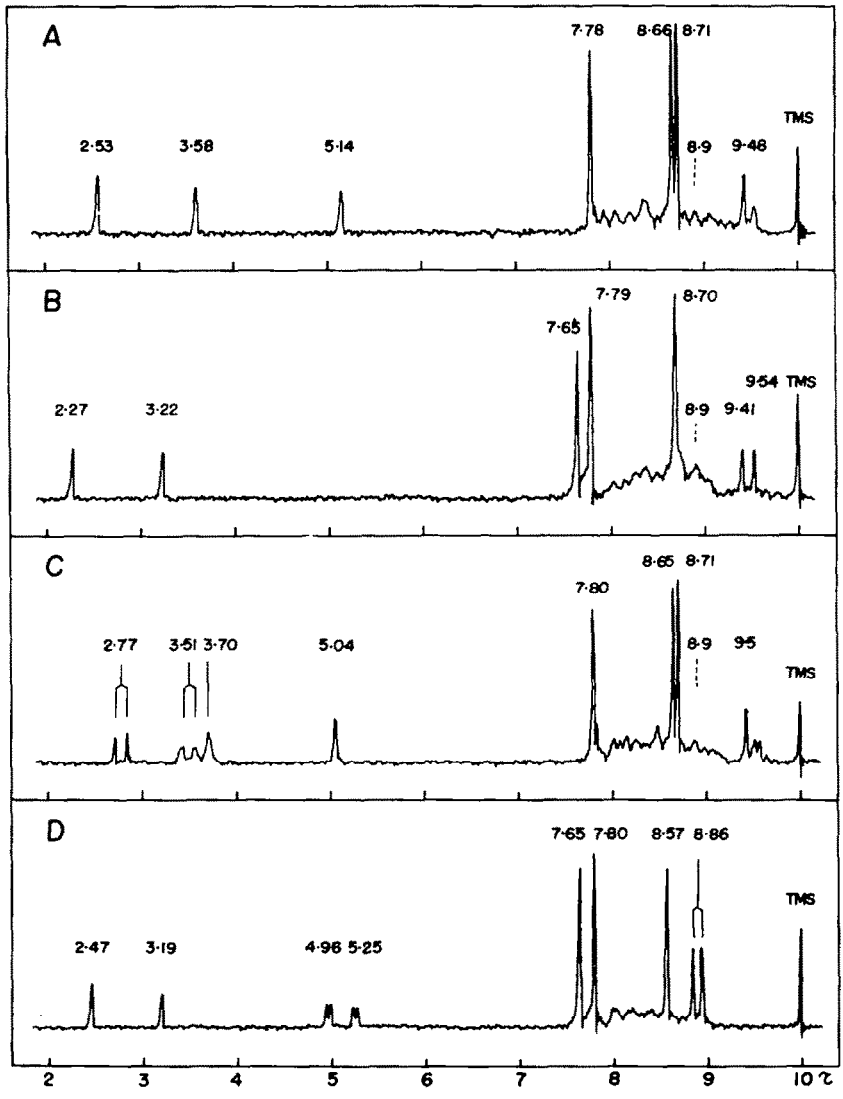
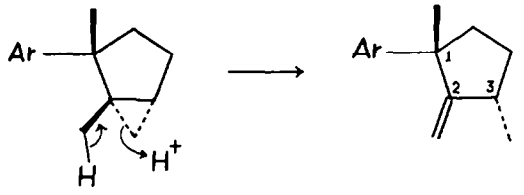


FIG 1. NMR spectra of (A) laurinterol, (B) laurinetrol acetate, (C) debromolaurinterol and (D) isolaurinterol acetate.

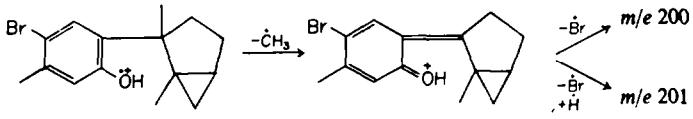
(10:1) eluate in the chromatography of the phenol acetate mixture. The IR and NMR (Fig 1-D) spectra indicated the presence of a trisubstituted phenol acetate grouping similar to that of Ia (Fig 1-B) [ν_{max} 1772, 1610, 1200 and 1150 cm^{-1}; τ 7·65 (3H, s), 3·19 (1H, s) and 2·47 (1H, s)], an aromatic Me [τ 7·80 (3H, s)], a tertiary Me [τ 8·57 (3H, s)], a secondary Me [τ 8·86 (3H, d, J = 6·5 c/s)] and an exomethylene group [ν_{max} 1650 and 890 cm^{-1}; τ 5·25 and 4·96 (each 1H, d, J = 3 c/s)]. From these data, it was suggested that isolaurinterol acetate would possess structure IIIa. This acetate on mild hydrolysis gave the corresponding phenol, isolaurinterol (III), $C_{15}H_{19}OBr$, as colourless oil (ν_{max} 3480, 3100, 1640 and 875 cm^{-1}) which was readily converted into

aplysin (V) by the treatment with *p*-toluenesulfonic acid in acetic acid supporting the structure III for isolaurinterol. It is noteworthy that the disposition of the exocyclic methylene group (at C-2) and the secondary Me (at C-3) is in reverse order to that of laurene, a sesquiterpene from *L. glandulifera*.[6] In view of the fact that isolaurinterol (III) is isolated together with laurinterol (I) from the same alga, natural occurrence of III would be explicable by the biogenetical scheme shown in the following.

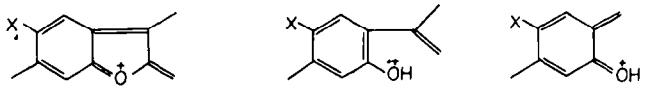


Furthermore, upon repeated rechromatographies of the fraction eluted with n-hexane–benzene (3:1) mentioned above, a new compound has been isolated in small quantities along with Ia. This compound, IVa, could be assumed to be a debromo analog of isolaurinterol acetate from its NMR spectral data (Experimental). An attempt to isolate debromoisolaurinterol (IV) in pure state from IVa failed because it is unstable towards acid and only a small quantity of IVa was available.

The mass spectrum of laurinterol (Fig 2-A) shows several remarkable peaks at *m/e* 281 and 279 (100), 239 and 237 (65), 228 and 226 (75), 201 and 199 (55?), 200 (65), 159 (60), 148 (40) and 121 (18), which would be assigned as follows.



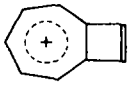
a: *m/e* 296, 294 **b**: *m/e* 281, 279 **c**



d **e** **f**

X = Br: *m/e* 239, 237 X = Br: *m/e* 228, 226 X = Br: *m/e* 201, 199
X = H: *m/e* 159 X = H: *m/e* 148 X = H: *m/e* 121

A peak at *m/e* 115 (52) could be attributed to formation of a stable cation (**g**).



(**g**) *m/e* 115

Similar fragmentations were observed in the spectra of debromolaurinterol (Fig 2-B) and its acetate (Fig 2-C) [*m/e* 201 (II, 100; IIa, 100), 175 (67; 94), 159 (75; 74), 148 (78; 91), 121 (58; 51) and 115 (40; 24)] and of isolaurinterol acetate (Fig 2-D).

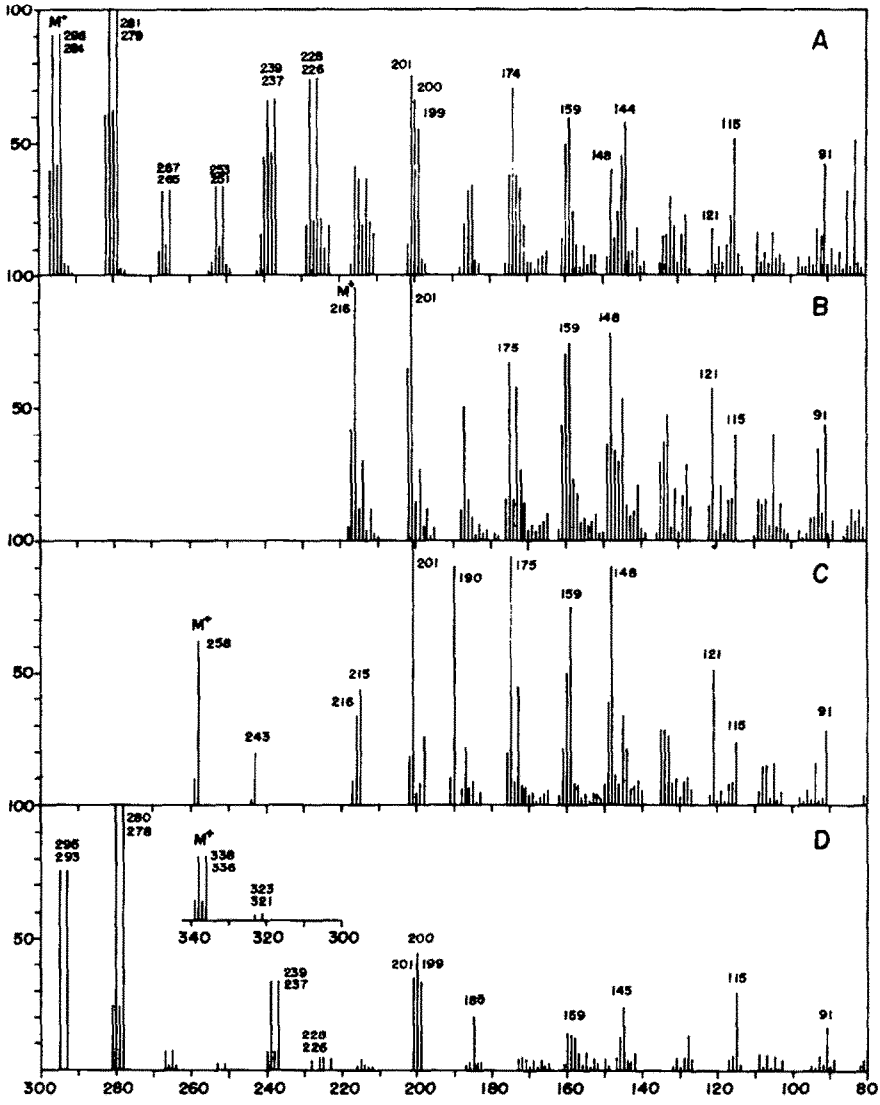


FIG 2. Mass spectra of (A) laurinterol, (B) debromolaurinterol, (C) debromolaurinterol acetate and (D) isolaurinterol acetate.

EXPERIMENTAL

All the m.ps are uncorrected. The purity of each compound was always checked by TLC. The UV and IR spectra were measured using Hitachi spectrophotometer and Nippon-Bunko 402-G or IR-S spectrophotometer, respectively. The NMR measurements were performed in CCl_4 with Nippon-Denshi 60 Mc spectrometer, TMS being used as an internal reference. Rotations were measured in $CHCl_3$ soln.

Isolation. Air dried seaweed (0·9 kg), collected in August at Oshoro Bay, Hokkaido, was extracted with MeOH and the MeOH soln was concentrated *in vacuo*. The residue was percolated with ether and the ether soln was shaken with 5% KOHaq and then with 1N HCl to remove acidic and basic compounds. After evaporation of the solvent, neutral, brown coloured oil (10 g) was obtained. Laurinterol (I) was isolated

in pure state by repeated careful chromatographies of the neutral fraction. However, the isolation and purification of I was reached more easily via its acetate. The neutral fraction mentioned above was chromatographed on alumina, and the fraction (3·2 g) eluted with n-hexane–benzene (5:1) was acetylated with acetic anhydride and pyridine in the usual manner. The acetylated product was chromatographed over silica gel. Fraction eluted with n-hexane–benzene (3:1) on removal of the solvent left a crystalline substance. Recrystallization from MeOH gave laurinterol acetate (Ia: 1·5 g) as colourless crystals, m.p. 93–93·5°; $[\alpha]_D$ + 11·1°(*c*, 1·53; Chf); UV, λ_{max}^{EtOH} 270 and 278 mμ (ε 670 and 660); IR, ν_{max}^{Nujol} 3060, 1765, 1200, 1160, 1065, 1020 and 920 cm^{-1}; NMR, τ 9·54 (1H, br. s), 9·41 (1H, br. s), ca. 8·9 (1H, m), 8·70 (6H, s), 7·79 (3H, s), 7·65 (3H, s), 3·22 (1H, s) and 2·27 (1H, s). (Found: C, 60·32; H, 6·27. $C_{17}H_{21}O_2Br$ requires: C, 60·54; H, 6·28%).

Hydrolysis of Ia with MeOH-KOH gave laurinterol (I), m.p. 54–55° (from MeOH); $[\alpha]_D$ +13·3° (*c*, 1·88; Chf); UV, λ_{max}^{EtOH} 225, 283 and 289 mμ (ε 7100, 2200 and 2100); IR, ν_{max}^{Chf} 3600, 3450, 3060, 1610, 1495, 1152, 1080, 1025, 900, 865 and 850 cm^{-1}; NMR, τ 9·48 (2H, br. d, J = 6·5 c/s), ca. 8·9 (1H, m), 8·71 (3H, s), 8·66 (3H, s), 7·78 (3H, s), 5·14 (1H, s), 3·58 (1H, s) and 2·53 (1H, s); mass, *m/e* (rel. abund.) 296 and 294 (M^+), 281 and 279 ($M^+ - CH_3$; 100), 267 and 265 (32), 253 and 251 (32), 239 and 237 (65), 228 and 226 (75), 215 ($M^+ -$ Br; 35), 201 (72), 200 (65), 199 (55), 174 (67), 159 (60), 148 (40), 144 (58), 121 (18), 115 (52), 91 (45), 83 (52), 77 (30), 74 (72), 59 (82) and 45 (78).

Fraction eluted with n-hexane–benzene (1:1) gave an oily substance, which was purified by rechromatography over silica gel to give debromolaurinterol acetate (IIa; 1 g), colourless oil, $[\alpha]_D$ −28·9° (*c*, 2·04; Chf); UV, λ_{max}^{EtOH} 263 and 272 mμ (ε 450 and 470); IR, ν_{max}^{film} 3060, 1770, 1757, 1620, 1570, 1505, 1450, 1375, 1200, 1160, 1132, 1020, 957, 900, 860 and 822 cm^{-1}; NMR, τ ca. 9·5 (2H, m), ca. 8·9 (1H, m), 8·70 (6H, s), 7·82 (3H, s), 7·68 (3H, s), 3·19 (1H, br. s), 3·15 (1H, br. d, J = 7·5 c/s) and 2·53 (1H, d, J = 7·5 c/s); mass, *m/e* (rel. abund.) 258 (M^+), 243 ($M^+ - CH_3$; 20), 215 ($M^+ - CH_3CO$; 45), 201 (100), 190 (91), 175 (94), 160 (50), 159 (74), 148 (91), 121 (51), 115 (24), 91 (28), 77 (21), 74 (25), 59 (31), 45 (24) and 43 (45).

Hydrolysis of IIa gave an oily substance, which was purified by chromatography over silica gel to give debromolaurinterol (II), colourless oil, $[\alpha]_D$ −12·2° (*c*, 1·80; Chf); UV, λ_{max}^{EtOH} 276 and 282 mμ (ε 3500 and 3400); IR, ν_{max}^{film} 3580, 3060, 1620, 1580, 1520, 1420, 1392, 1378, 1295, 1230, 1185, 1130, 1100, 1060, 1020, 955, 855 and 815 cm^{-1}; NMR, τ ca. 9·5 (2H, m), ca. 8·9 (1H, m), 8·71 (3H, s), 8·65 (3H, s), 7·80 (3H, s), 5·04 (1H, s), 3·70 (1H, br. s), 3·51 (1H, br. d, J = 7·5 c/s) and 2·77 (1H, d, J = 7·5 c/s); mass, *m/e* (rel. abund.) 216 (M^+), 201 ($M^+ - CH_3$; 100), 187 (51), 175 (67), 173 (58), 160 (70), 159 (75), 148 (78), 145 (55), 121 (58), 115 (40), 91 (44), 77 (40), 74 (52), 59 (57) and 45 (53).

Fraction eluted with n-hexane–benzene (10:1) left an oily substance, which was purified by rechromatography over silica gel to give isolaurinterol acetate (IIIa; 50 mg), colourless oil, $[\alpha]_D$ −70° (*c*, 1·42; Chf); IR, ν_{max}^{film} 3100, 1772, 1650, 1610, 1200, 1150, 1020, 905 and 890 cm^{-1}; NMR, τ 8·86 (3H, d, J = 6·5 c/s), 8·57 (3H, s), 7·80 (3H, s), 7·65 (3H, s), 5·25 (1H, d, J = 3 c/s), 4·96 (1H, d, J = 3 c/s), 3·19 (1H, s) and 2·47 (1H, s); mass, *m/e* (rel. abund.) 338 and 336 (M^+), 323 and 321 ($M^+ - CH_3$; 2), 295 and 293 ($M^+ - CH_3CO$; 75), 280 and 278 ($M^+ - CH_3 - CH_3CO$; 100), 239 and 237 (33), 228 and 226 (5), 201 and 199 (35), 200 (45), 185 (22), 145 (25), 115 (30), 91 (18), 77 (10), 74 (15), 59 (19), 58 (28) and 43 (40). Hydrolysis of IIIa (28 mg) afforded isolaurinterol (III; 20 mg), colourless oil, IR, ν_{max}^{film} 3480, 3100, 1640, 1610, 1160, 900 and 875 cm^{-1}.

Debromoisolaurinterol acetate (IVa) was isolated in small quantities together with Ia; NMR, τ 8·83 (3H, d, J = 6 c/s), 8·55 (3H, s), 7·77 (3H, s), 7·65 (3H, s), 5·23 (1H, d, J = 3 c/s), 4·95 (1H, d, J = 3 c/s), 3·25 (1H, br. s), 3·15 (1H, br. d, J = 11 c/s) and 2·75 (1H, d, J = 11 c/s).

Conversion of laurinterol (I) *to debromolaurinterol* (II). To a soln of I (32 mg) in THF (20 ml) was added LAH (100 mg), and the mixture was refluxed for 40 hr, cooled and mixed with water. After filtration and evaporation of the filtrate *in vacuo*, the residue was repeatedly extracted with ether and the ether soln was dried over Na_2SO_4 and evaporated. The resulting oily substance was purified by chromatography on alumina (standard) to give colourless oil (20 mg), $[\alpha]_D$ −12°. The IR and NMR spectra were superimposable over those of II.

Conversion of debromolaurinterol (II) *to laurinterol acetate* (Ia). One molecular equivalent of Br_2 (31 mg) in AcOH (5 ml) was added to an ice-cold soln of II (42 mg) in the same solvent (1 ml) under continuous stirring. The mixture was then allowed to stand at room temp for 30 min and then extracted with ether. The ether soln was washed four times with 15 ml portions of water, two times with 10 ml portions of 5% $NaHCO_3$ soln and finally with 15 ml of saturated NaCl soln and dried over Na_2SO_4. A crude substance obtained after removal of the solvent was chromatographed over silica gel to give colourless oil (39 mg), which was acetylated in the usual manner. The product, after purification by chromatography on silica gel, melted

at 92–93° and was identified as laurinterol acetate (Ia) by the mixed melting point method and a comparison of IR and NMR spectra.

Rearrangement of laurinterol (I) *to aplysin* (V). A soln of I (110 mg) and *p*-TsOH (25 mg) in glacial AcOH (2 ml) was heated at 50° for 65 hr. After being cooled, the reaction mixture was poured into water (5 ml) and the whole was repeatedly extracted with ether. The ether soln was washed two times with 10 ml portions of water, three times with 10 ml portions of 5% $NaHCO_3$ soln and finally with 15 ml of saturated NaCl soln, and dried over Na_2SO_4. Crude crystals obtained after removal of the solvent were recrystallized from MeOH to give aplysin (V; 100 mg), m.p. and mixed m.p. 85–86°, $[\alpha]_D$ −86·1° (c, 1·31; Chf); IR, ν_{max}^{Nujol} 1615, 1580, 1488, 1265, 1230, 1008, 860 and 780 cm^{-1}; NMR, τ 8·97 (3H, d, J = 6 c/s), 8·80 (3H, s), 8·73 (3H, s), 7·76 (3H, s), 3·60 (1H, br. s) and 3·08 (1H, br. s).

Rearrangement of debromolaurinterol (II) *to debromoaplysin* (VI).[5] A soln of II (51 mg) and *p*-TsOH (25 mg) in glacial AcOH (2 ml) was heated at 50° for 25 hr. After being worked up as mentioned above debromoaplysin (VI; 47 mg), colourless oil $[\alpha]_D$ −61° (c, 0·74; Chf), was obtained. IR, ν_{max}^{film} 1620, 1595, 1500, 1280, 1265, 1120, 1010, 950 and 800 cm^{-1}; NMR, τ 8·90 (3H, d, J = 6 c/s), 8·75 (3H, s), 8·70 (3H, s), 7·72 (3H, s), 3·60 (1H, br. s), 3·50 (1H, br. d, J = 7 c/s) and 3·20 (1H, d, J = 7 c/s); mass, *m/e* (rel. abund.) 216 (M^+; 36), 201 ($M^+ - CH_3$; 100), 187 (11), 173 (18), 160 (31), 159 (50), 145 (14), 115 (9), 91 (9), 77 (6), 43 (5) and 41 (8).

Rearrangement of isolaurinterol (III) *to aplysin* (V). A soln of III (20 mg) and *p*-TsOH (25 mg) in glacial AcOH (2 ml) was heated at 45° for 45 hr. After being cooled, the reaction mixture was poured into water and worked up as in the case of I to give pure V (19 mg).

Acknowledgements—The authors wish to express their thanks to Professor Yoshimasa Hirata, Nagoya University, for providing them with aplysin, and to Dr. Hiroshi Yabu and Dr. Iemasa Yamada for collecting the seaweed. The authors' thanks are also due to Mr. Shigezo Shimokawa for the NMR measurements and to Professor Koshiro Miyahara for measurements of mass spectra.

REFERENCES

[1] Part XVI of "Constituents from Marine Plants". Part XV, T. Irie, M. Izawa and E. Kurosawa, *Tetrahedron* **26**, 851 (1970)
[2] T. Irie, M. Suzuki, E. Kurosawa and T. Masamune, *Tetrahedron Letters* 1837 (1966)
[3] S. Yamamura and Y. Hirata, *Tetrahedron* **19**, 1485 (1963)
[4] A. F. Cameron, G. Ferguson and J. M. Robertson, *Chem. Commun.* 271 (1967); *J. Chem. Soc.* B, 692 (1969)
[5] T. Irie, M. Suzuki and Y. Hayakawa, *Bull. Chem. Soc. Japan* **42**, 843 (1969)
[6] T. Irie, T. Suzuki, Y. Yasunari, E. Kurosawa and T. Masamune, *Tetrahedron* **25**, 459 (1969)